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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,713	01/22/2002	Andrew Jamieson	8325-0026	6239

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EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/055,713	JAMIESON ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 17, 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed December 17, 2003 has been entered.

Pages 7, 10 and 19 of the specification have been amended.

Claim 20 is cancelled.

Claims 1, 12 and 17 are currently amended.

Claims 1-19 are pending and are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

Claims 1-19 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant points out that there is both a known and disclosed correlation between zinc finger protein structure and binding function, as well as a clear description in the specification of how to make the claimed zinc finger proteins, and argues that these facts combined with the

description in the specification of an entire genus of zinc finger proteins adequately describes the claimed molecules. (reply pages 5-6)

The Examiner acknowledges that there is both a known and disclosed correlation between zinc finger protein structure and binding function, but maintains that this correlation is not sufficient to describe the structural features of the claimed invention. The claimed invention is directed to plant zinc finger proteins that are modified, and neither known nor disclosed correlations between zinc finger protein structure and binding function serve to describe how the claimed plant zinc finger proteins have been modified. Furthermore, the description in the specification of how to make modified finger proteins combined with the description in the specification of an entire genus of zinc finger proteins does not adequately the claimed modified plant zinc finger proteins, because the specification does not describe how to make all possible modifications to all types of plant zinc finger proteins, and because the described genus is not commensurate in scope with the claimed genus.

Applicant additionally points out that the rejected claims recite both structure (modified plant zinc finger protein that is non-naturally occurring and engineered) and function (binding to a target sequence), and further argues that the skilled artisan would have recognized from the disclosure that Applicant was in possession of the claimed subjected matter at the time of filing. Applicant also argues that the disclosed genus of proteins is an amply representative number of species to support the description of the claimed genus, and that it is well within the purview of one skilled in the art to determine other embodiments falling within the scope of the claims. (reply pages 6-8)

The Examiner maintains that the recited structure and function are both indefinite and non-specific. The claims recite no limitations that distinguish a zinc finger protein from other proteins, or that distinguish a plant zinc finger protein from other zinc finger proteins, or that distinguish the alterations that are characteristic of the claimed proteins. Only dependent claims 2-4 recite any limitations that indicate the specific nature of the target sequence bound. Additionally, possession of the claimed subjected matter at the time of filing does not substitute for a description of the claimed subjected matter, and the subject matter possessed by Applicant is not commensurate in scope with the claimed subject matter.

Applicant asserts that the claimed modified plant zinc finger proteins do not have undefined structure, because multiple aspects of the structure of the zinc finger are disclosed in the specification, as are exemplary zinc finger sequences and modifications. Applicant further points out that "modified plant zinc finger protein" is defined in the specification. Applicant also asserts that the claimed proteins do not bind to undefined target sequences of any size and nature, because the proteins may be engineered to bind to any target sequence of choice. Applicant additionally asserts that the claimed proteins do not further encode a domain of undefined structure and function that may repress or activate some unknown process, because the term "functional domain" is defined in the specification as a protein or polypeptide that has transcriptional modulation activity or is capable of interacting with proteins or domains having transcriptional modulation activity (reply pages 8-9).

The Examiner maintains that the claimed modified plant zinc finger proteins do have undefined structure, because the claims recite no specific limitations that indicate how the plant

zinc finger protein is modified. The specific protein modifications that are proposed or exemplified in the specification do not specifically limit "modified" in the rejected claims. The Examiner also maintains that the claimed proteins do bind to undefined target sequences, as only dependent claims 2-4 recite any limitations that indicate the nature of the target sequence, and these limitations (nucleic acid sequence, DNA, 3 or more contiguous nucleotides) are nonspecific. The Examiner further maintains that the claimed proteins do further encode a domain of undefined structure and function that may repress or activate some unknown process, because the claims recite no specific limitations that indicate the specific structural or functional characteristics of the functional domain. The specific functional domains that are disclosed or exemplified in the specification do not specifically limit "functional domain" in the rejected claims.

Applicant also argues that the citation of *Eli Lilly* is also misplaced because the disclosure and the state of the art in *Eli Lily* are entirely different from those in the case at hand, as the specification at issue in *Eli Lily* did not disclose any structure at all in support of the description of the claimed molecules (reply pages 9-10).

The Examiner maintains that the citation of *Eli Lilly* is germane to the instant rejection because the case provides guidance with respect to how a genus of nucleic acid coding sequences may be described.

Claims 1-19 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polynucleotides encoding the exemplified genus

of modified plant zinc finger proteins, does not reasonably provide enablement for isolated polynucleotides encoding plant zinc finger proteins of having any and all structural configurations and modifications that bind to target sequences of any size and any nature. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant argues that the rejected claims are not directed to plant zinc finger proteins of undefined structure and unknown modification that bind to target sequences of any size and any nature, but are rather directed to non-naturally-occurring proteins with modifications in the spacing and/or backbone sequence of a plant zinc finger in which one or more of the zinc fingers are engineered such that the protein binds a target site. (reply pages 10-11)

The Examiner maintains that none of the rejected claims make any reference to modifications in the spacing and/or backbone sequence of a plant zinc finger. Also, no claim requires that "one or more of the zinc fingers" are engineered such that the protein binds a target site; the claims require only that the zinc finger protein itself be so engineered. Additionally, only dependent claims 2-4 recite any limitations that indicate the nature of the target sequence. Further, while dependent claims 5, 9 and 10 make general reference to structural features commonly associated with zinc finger proteins, and while dependent claims 12 and 13 make general reference to structural features commonly associated with the alteration of an amino acid

sequence, none of the rejected claims recite any limitations that specifically indicate how the claimed zinc finger protein is engineered.

Applicant also argues that undue experimentation is not required to practice the claimed invention because the specification provides ample details regarding the nature of non-canonical zinc finger proteins as well as their design, selection and incorporation into the claimed modified plant zinc finger protein. Applicant further points out that the production of non-canonical zinc finger is well known in the art, and argues that only routine experimentation would be required for one skilled in the art to incorporate non-canonical zinc fingers into the claimed modified plant zinc finger protein. (reply pages 11-12)

The Examiner maintains that undue experimentation would be required to practice the claimed invention because the specification does not provide guidance for making modified non-canonical plant zinc finger proteins. That non-canonical zinc finger proteins are known in the art, and that modified non-plant non-canonical zinc finger proteins have been produced, does not provide sufficient guidance to enable the full scope of the claimed invention, because the production of functional modified plant non-canonical zinc finger proteins is unpredictable. The specification does not explain how to alter the structure of the zinc finger backbone of any particular non-canonical plant zinc finger protein relative to any particular corresponding established non-canonical zinc finger standard.

Applicant additionally argues that the pending claims are not directed to molecules having undefined structure or unknown modification, as the specification discloses an entire

genus of molecules that fall within the scope of the claims. Applicant points out that time-consuming or expensive experimentation is not undue if routine. Applicant also points to the holding in *United States v. Telectonics Inc.* that the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, and argues that in the instant case the claimed invention is fully enabled as the specification exemplifies an entire genus of embodiments, as well as disclosing methods for determining other embodiments. (reply page 12)

The Examiner maintains that the claimed modified plant zinc finger proteins do have undefined structure, because the claims recite no specific limitations that indicate how the plant zinc finger protein is modified. The specific protein modifications that are proposed or exemplified in the specification do not specifically limit "modified" in the rejected claims. Additionally, the Examiner's assertion that undue experimentation would be required to practice the full scope of the claimed invention is not predicated on the time or cost of the required experimentation, but on its unpredictability. The holding in *United States v. Telectonics Inc.* is further not germane to the enablement of the instant invention, as the invention at issue in *United States v. Telectonics Inc.* (stainless steel electrodes) is not analogous to the instant invention. In the instant case the Examiner maintains that the full scope of the claimed invention is not enabled because the exemplified genus is not commensurate in scope with the claimed genus, and because making and using polynucleotides encoding polypeptides commensurate in scope with the claimed genus is unpredictable.

Applicant further argues that the claimed invention is fully enabled with respect to functional domains, as the specification provides extensive guidance on various functional domains other than those exemplified. Applicant additionally points out that, in addition to exemplifying the VP16 functional domain, all constructs tested in the Examples included the maize C1 activation domain as well. Applicant also asserts that it is irrelevant that some functional domains may be more or less effective in certain cell types, as a functional domain may not even be necessary to achieve the desired result of modulating gene expression. Applicant further argues that only routine experimentation would be required to determine suitable functional domains, and that the passage cited from Segal is speculative, and limited to *Arabidopsis* in particular rather than plants in general. (reply pages 12-13)

The Examiner maintains that it would require undue experimentation to make and use polynucleotides encoding modified plant zinc finger proteins that further comprise any type of functional domain, including any type of repressive or activation domain, because the specification does not provide sufficient guidance with respect to which functional domains would be operable in conjunction with a modified plant zinc finger protein and which would not. The disclosure of known functional domains other than those exemplified does not provide sufficient guidance, because the operability of many of the disclosed functional domains in plant cells is unpredictable and has not been established.

The Examiner also maintains that the ability of a functional domain to function in a particular cell type is relevant, because the presence of an encoded functional domain is required by claims 14-15. The Examiner further maintains that the passage cited from Segal et al. is

relevant to the enablement of the claimed invention and is not limited to *Arabidopsis*. Segal et al.'s assertion that the mammalian KRAB repressor domain would be a poor candidate for gene regulation in plants may be speculative, but Segal et al. support their assertion with specific facts. Segal et al.'s assertion is supported in general by the fact that repressor domain function is known to involve specific interactions between the repressor domain and other cellular proteins that may not be present in specific cell types or in the cells of other species of organisms, and in particular by the fact that the KRAB repressor domain is not found in *Drosophila melanogaster, Caenorhabditis elegans, Saccharomyces cerevisiae or Arabidopsis thaliana*. The assertion that the mammalian KRAB repressor domain would be a poor candidate for gene regulation in plants is therefore reasonable, given the diversity of non-mammalian species that lack the mammalian KRAB repressor domain, and that therefore also potentially lack the proteins it would require to effect its function.

Claims 1 and 17 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "target sequence", for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant traverses the rejection because "target sequence" is defined in the specification, for example at page 16 lines 9-15 (reply page 13).

The rejection is maintained because the discussion of target sequences in the specification does not limit the term "target sequence" in the rejected claims.

Claim 14 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "functional domain", for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant traverses the rejection because "functional domain" is defined in the specification, for example at page 15 lines 19-25, and because exemplary functional domains are disclosed at page 22 line 30 through page 24 line 12 (reply page 14).

The rejection is maintained because the discussion of functional domains and the exemplary functional domains disclosed in the specification do not limit the term "functional domain" in the rejected claim.

Claim 15 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "repressive domain", for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant traverses the rejection because repressive domain would readily be understood by the skilled artisan in light of the disclosure, for example at page 22 lines 23-27, and at page 22 line 30 through page 23 line 6 (reply page 14).

The rejection is maintained because the discussion of repressive domains in the specification does not limit the term "repressive domain" in the rejected claim.

Claim 16 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "activation domain", for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant traverses the rejection because activation domain is definite in view of the disclosure, for example at page 22 lines 23-27, and page 23 line 19 through page 24 line 7 (reply page 14)

The rejection is maintained because the discussion of activation domains in the specification does not limit the term "activation domain" in the rejected claim.

Claim 17 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "modified", for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant traverses the rejection because modified is defined and described in the specification, for example at page 10 lines 17-24 page 18 line 19 through page 21 line 15 Applicant additionally points to the normal meaning of "variant" and "derived" in support of the definiteness of the rejected claim, and the definition of "target sequence" in the specification discussed *supra* (reply pages 14-15).

The rejection is maintained because the discussion of modifications in the specification does not limit the term "modified" in the rejected claim. Furthermore, that "variant" and "derived" are to be given their normal meaning (something that differs in form only slightly from something else, and received or obtained from a source respectively) does not clarify what would constitute an amino acid sequence "variant", or how sequences would be "derived" from plant sources. Additionally, "target sequence" is considered to be indefinite as discussed *supra*.

Claim Rejections - 35 USC § 102

Claims 1-4, 14 and 16-19 remain rejected under 35 U.S.C. 102(b) as being anticipated by Aoyama et al. (The Plant Journal, 1997, Vol. 11, No. 3, 605-612), for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant argues that the rejection should be withdrawn in light of the amendment of claim 1 to recite that the zinc finger protein is "non-naturally occurring" and "engineered to bind to a target sequence", in contrast to the zing finger portion of the protein taught by Aoyama et al., which protein comprises a naturally occurring non-engineered yeast GAL4 zinc finger protein (reply page 15).

The rejection is maintained because the limitations "non-naturally occurring" and "engineered to bind to a target sequence" do not impose any specific structural or functional characteristics on the claimed zinc finger protein that would distinguish the claimed zinc finger protein from the protein taught by Aoyama et al. The protein taught by Aoyama et al. is "non-

naturally occurring" because it is a fusion protein comprising the DNA-binding domain of the yeast GAL4 zinc finger transcription factor, the transactivating domain of the herpes viral protein VP16, and the receptor domain of the rat glucocorticoid receptor (page 605 column 2 last paragraph through page 606 column 2 first full paragraph and Figure 1; page 608 Figure 3). Such a protein does not occur in nature. The protein taught by Aoyama et al. is "engineered to bind to a target sequence" because it is genetically engineered for the purpose of activating transcription by binding to the GAL4 upstream activating sequence. The protein taught by Aoyama et al. is also "engineered to bind to a target sequence" in that it was evolutionarily engineered for this function by the process of natural selection.

Claims 1-9 and 12-19 remain rejected under 35 U.S.C. 102(b) as being anticipated by Takatsuji et al. (J Biol Chem. 1996 Sep 20; 271(38):23368-73), for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant argues that the rejection should be withdrawn because the claims are drawn to non-naturally-occurring, engineered, modified zinc finger proteins, in contrast to the protein taught by Takatsuji et al., which is entirely naturally-occurring and non-engineered. Applicant additionally points out that the binding characteristics of the EPF protein were tested against target sites that are referred to as "probes", and that only these "probes" were physically altered (mutated) by Takatsuji et al., not the EPF protein (reply pages 15-16).

It is acknowledged that the probes used by Takatsuji et al. were physically altered (mutated), but the Examiner disagrees with the assertion that Takatsuji et al. did not alter the EPF protein. See for example page 133, column 2, third full paragraph, which recites "we characterized DNA-protein interaction using wild-type and mutated recombinant EPF proteins" and "site-directed mutagenesis of the EPF protein revealed that the two zinc fingers act synergistically". See also for example page 23372 column 1 and Figure 7, which disclose the effect of substituting the first histidine to asparagine in the first zinc finger or the second zinc finger of the EPF protein. See additionally for example *Construction of Plasmids*, pages 23368-23369, which describes the construction of plasmids for the production of truncated forms of the EPF protein. Accordingly, the rejection is maintained.

Claims 1-8, 10 and 17 remain rejected under 35 U.S.C. 102(e) as being anticipated by Coupland et al. (U.S. Patent No. 6,077,994 A, filed October 20, 1997 and issued June 20, 2000), for the reasons of record set forth in the office action mailed October 1, 2003.

Applicant's arguments filed December 17, 2003, have been fully considered but they are not persuasive.

Applicant argues that the rejection should be withdrawn in light of the amendment of claim 1 to recite that the zinc finger protein is "non-naturally occurring" and "engineered to bind to a target sequence", in contrast to the zing finger protein taught by Coupland et al., which is a naturally-occurring non-engineered zinc finger protein (reply page 16).

The rejection is maintained because the limitations "non-naturally occurring" and "engineered to bind to a target sequence" do not impose any specific structural or functional

characteristics on the claimed zinc finger protein that would distinguish the claimed zinc finger protein from proteins taught by Coupland et al. In addition to teaching a naturally-occurring non-engineered CONSTANS zinc finger protein, Coupland et al. also teach "non-naturally occurring" zinc finger proteins in that Coupland et al. teach mutants, derivatives and alleles which encode a protein which retains a functional characteristic of the CONSTANS protein encoded by the wild-type gene, especially the ability to promote flowering, as well as mutants, derivatives and alleles which encode a protein which delays flowering compared to wild-type or a gene with the sequence provided (column 2 lines 9-18). Coupland et al. teach that changes to a sequence, to produce a mutant or derivative, may be by one or more of addition, insertion, deletion or substitution of one or more nucleotides in the nucleic acid, leading to the addition, insertion, deletion or substitution of one or more amino acids in the encoded polypeptide (column 2 lines 18-23). Such proteins do not occur in nature. The protein taught by Coupland et al. is "engineered to bind to a target sequence" in that it was evolutionarily engineered for this function by the process of natural selection.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CC

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